

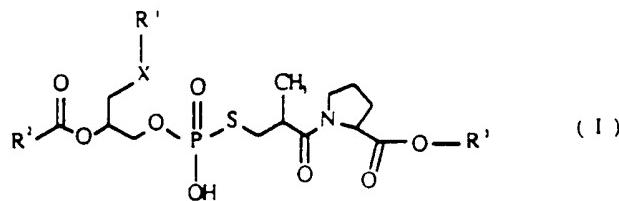
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(54) Title: NEW PYRROLIDINE DERIVATIVES



(57) Abstract

This invention relates to new pyrrolidine derivatives represented by formula (I) as below, having superior pharmacological activity as antihypertensive agents (I) wherein R^1 is saturated or unsaturated alkyl of 2 to 20 carbon atoms, or aryl group; R^2 is saturated or unsaturated alkyl of 1 to 17 carbon atoms, or aryl group; R^3 is hydrogen atom, saturated or unsaturated alkyl of 1 to 20 carbon atoms, or aryl group or its derivatives; and X is oxygen or sulfur atom.

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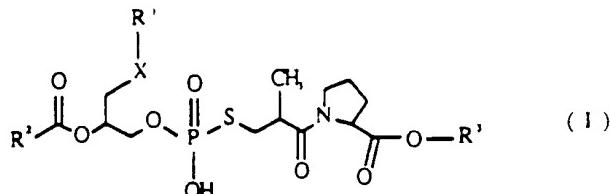
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1
NEW PYRROLIDINE DERIVATIVES

TECHNICAL FIELD

This invention relates to new pyrrolidine derivatives represented by general formula(I) as below and their pharmacologically acceptable salts which are useful as antihypertensive



wherein,

- 10 R¹ is saturated or unsaturated alkyl of 2 to 20 carbon atoms, or aryl group;
- R² is saturated or unsaturated alkyl of 1 to 17 carbon atoms, or aryl group;
- R³ is hydrogen atom, saturated or unsaturated alkyl of 1 to 20 carbon atoms, or aryl group or its derivatives; and
- X is oxygen or sulfur atom.

15

BACKGROUND OF THE INVENTION

Platelet activating factor(PAF) was first identified in 1979 to be 1-O-alkyl-2-O-acetyl-sn-glycerol-3-phosphocholine by Benveniste et al. [C. R. Acad. Sci., Paris(D), 289, 1037-1040(1979)].

- 20 It was also reported that this PAF produces a variety of physiological responses such as platelet activation and antihypertension. The conjugates of nucleosides with PAF derivatives or with their analogues have been reported to exhibit diverse pharmacological activities such as anticancer, antiinflammation and antivirus activity in literatures [Journal of Medicinal Chemistry, 25, 1322(1982), Biochemical and Biophysical Research Communication, 85, 715(1978), Biochimica et Biophysica Acta, 69, 604(1980), J. Med. Chem., 28(2), 171-7(1985), Ibid., 31(9), 1793-8(1988), Ibid., 33(5), 1380-6(1990)].
- 25

Most of the antihypertensive agents, so far used in medicine have to be taken

2

orally or by intravenous administration and the dosage has to be repeatedly administered to maintain proper plasma concentration of a drug.

However to achieve and maintain a plasma concentration of drug within the therapeutical range is not easy. If the plasma concentration of drug remains high it leads
5 to related side effects and development of tolerance to the drug. The problem of economy of long term oral therapy also can not be disregarded.

Development of transdermal therapeutic mode of delivery of antihypertensive agent with favorable pharmacokinetic parameters maintained for a long duration time, with improved convinience and patient compliance, and with minimal side effects has
10 been for long considered necessary.

SUMMARY OF THE INVENTION

The objective of this invention is to provide new pyrrolidine derivative antihypertensive compounds with convenient dosage regime compared to convenient
15 therapy, and superior therapeutic effect.

DETAILED DESCRIPTION OF THE INVNETION

This invention relates to new pyrrolidine derivatives shown by above formula (I) and especially new compounds having excellent physiological activities as
20 antihypertensive agent.

In the above formula(I), R¹ is octadecyl, cetyl, methyl, ethyl, dodecyloxy, methylphenyl or sulfonyloctyl group ; R² is methyl, ethyl, propyl, butyl, heptadecyl, pentadecyl, oleyl or cetyl group ; R³ is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, pentyl, cyclohexyl, benzoyl, benzyl, p-nitrobenzyl, p-toluenesulfonyl, p-methoxybenzyl,
25 2,4,6-trimethylbenzyl or phthalimidomethyl group.

The phospholipid part of above formula(I) consists either D, L or DL type of optical isomers and the part linked to phosphoric acid are angiotensin converting enzyme(ACE) inhibitors and their derivatives commonly used as antihypertensive agent.

Present invention also includes the compositions of above referred structure(I)

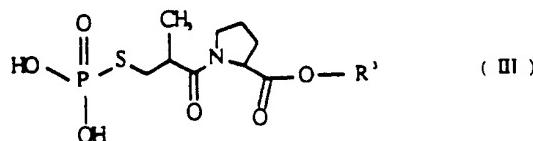
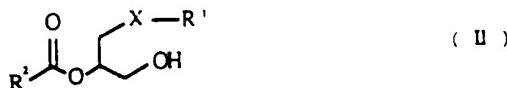
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antihypertensive agents in pharmaceutical dosage forms including transdermal therapeutic dosage form.

New pyrrolidine derivatives of this invention represented by formula(I) are new conjugates introducing ACE inhibitor into basic structure of glycerol. Specifically, 5 conjugates of 1-S- or 1-O-alkyl-2-O-acyl phospholipids are linked with ACE inhibitors or their derivatives by phosphate ester bond and resulting compounds are new synthetic compounds with favorable antihypertensive activity.

The methods for preparing new compounds of this invention are as follows:

New pyrrolidine derivatives and their salts of above formula(I) can be prepared 10 by condensation of compound(II) with compound of formula(III) using condensing agent in anhydrous basic solvent



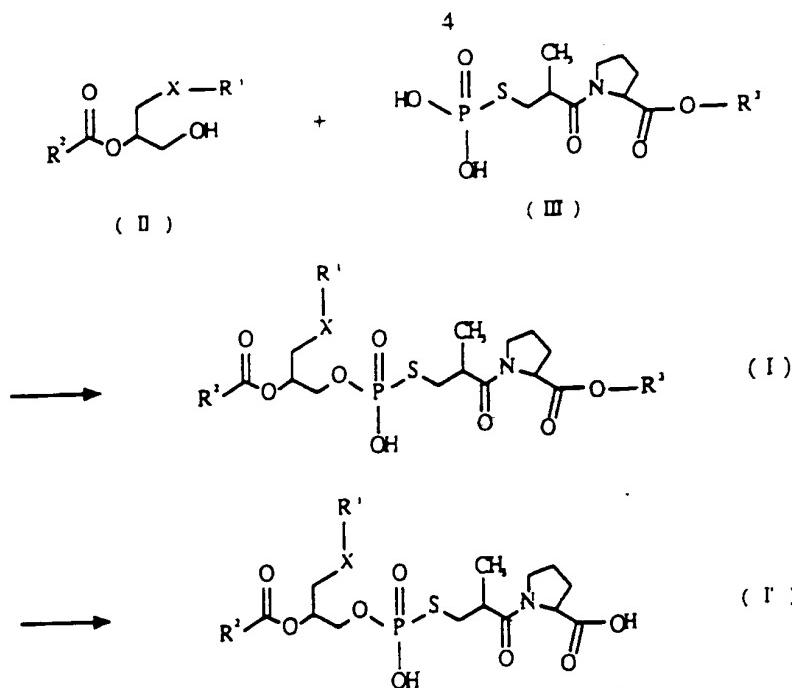
wherein,

15 R^1 and R^2 each are as defined in formula(I) above ; and

R^3 is saturated or unsaturated alkyl of 1 to 20 carbon atoms, or aryl group or its derivatives.

The products of formula (I) are produced by the method depicted in the following equations.

20 1-S-alkyl-2-O-acylthioglycerol or 1-O-alkyl-2-O-acylglycerol(II) is condensed with phosphoric acid compound(III) to give compound(I). Using the metallic catalyst, e.g., zinc, iron and nickel, formula (I) can be converted by conventional methods such as hydrolysis or hydrogenation to formula(I')



wherein,

R¹, R² and R³ are as defined previously.

In this invention the condensation reaction is conducted at 40~100°C. But it shall
5 be noted that higher temperature of reaction lead to unnecessary side reaction and if the
reaction temperature is kept low, the reaction does not proceed.

Within the scope of this invention, anhydrous bases are pyridine, triethylamine
and ethylamine, etc. The condensing agents in this synthetic route are dicyclohexyl-
carbodiimide, 2,4,6-triisopropylbenzenesulfonylchloride, 1-(2,4,6-triisopropylbenzene-
10 sulfonyl)imidazole, 1-(2,4,6-triisopropylbenzenesulfonyl)-3-nitro-1,2,4-triazole and 2-
ethoxy-1-(2H)-quinoline carboxylic acid ester.

The compounds of formula (I) and their salts in this invention can be used in
pharmaceutical formulations in combination with organic or inorganic vehicles. Their
salts are physiologically acceptable conventional salts.

15 They may be utilized in conventional types of pharmaceutical dosage forms such
as suspensions, emulsions, patches, powders, granules, capsules, tablets and pills,
containing commonly used components of pharmaceutical formulation, vehicle,
preservative, stabilizer, dispersant and adjuvants such as damping agent, emulsifier, filler

or buffer, colorant, etc., can be used.

In accordance with this invention, they can be formulated into patches, specially for transdermal therapeutic application.

Illustrative of new compound of formula (I) by this invention are the following:

- 5 rac-1-O-cetyl-2-O-acetylglyceryl-3-phosphoryl captopril-p-nitrobenzyl ester,
 rac-1-O-cetyl-2-O-acetylglyceryl-3-phosphoryl captopril ethyl ester,
 rac-1-O-cetyl-2-O-acetylglyceryl-3-phosphoryl captopril methyl ester,
 rac-1-O-cetyl-2-O-acetylglyceryl-3-phosphoryl captopril benzyl ester,
 rac-1-O-cetyl-2-O-acetylglyceryl-3-phosphoryl captopril benzoyl ester,
- 10 rac-1-O-cetyl-2-O-acetylglyceryl-3-phosphoryl captopril isopropyl ester,
 rac-1-O-cetyl-2-O-acetylglyceryl-3-phosphoryl captopril-n-butyl ester,
 rac-1-O-cetyl-2-O-acetylglyceryl-3-phosphoryl captopril-t-butyl ester,
 rac-1-O-cetyl-2-O-acetylglyceryl-3-phosphoryl captopril cyclohexyl ester,
 rac-1-O-cetyl-2-O-acetylglyceryl-3-phosphoryl captopril pentyl ester,
- 15 rac-1-O-cetyl-2-O-acetylglyceryl-3-phosphoryl captopril-p-toluenesulfonyl ester,
 rac-1-O-cetyl-2-O-acetylglyceryl-3-phosphoryl captopril-p-methoxybenzyl ester,
 rac-1-O-cetyl-2-O-acetylglyceryl-3-phosphoryl captopril-2,4,6-trimethylbenzyl ester,
 rac-1-O-cetyl-2-O-acetylglyceryl-3-phosphoryl captopril phthalimido methyl ester,
 rac-1-O-oleyl-2-O-palmitoylglyceryl-3-phosphoryl captopril-p-nitrobenzyl ester,
- 20 rac-1-O-oleyl-2-O-palmitoylglyceryl-3-phosphoryl captopril ethyl ester,
 rac-1-O-oleyl-2-O-palmitoylglyceryl-3-phosphoryl captopril methyl ester,
 rac-1-O-oleyl-2-O-palmitoylglyceryl-3-phosphoryl captopril benzyl ester,
 rac-1-O-oleyl-2-O-palmitoylglyceryl-3-phosphoryl captopril benzoyl ester,
 rac-1-O-oleyl-2-O-palmitoylglyceryl-3-phosphoryl captopril isopropyl ester,
- 25 rac-1-O-oleyl-2-O-palmitoylglyceryl-3-phosphoryl captopril-n-butyl ester,
 rac-1-O-oleyl-2-O-palmitoylglyceryl-3-phosphoryl captopril-t-butyl ester,
 rac-1-O-oleyl-2-O-palmitoylglyceryl-3-phosphoryl captopril cyclohexyl ester,
 rac-1-O-oleyl-2-O-palmitoylglyceryl-3-phosphoryl captopril pentyl ester,
 rac-1-O-oleyl-2-O-palmitoylglyceryl-3-phosphoryl captopril-p-toluenesulfonyl ester.

- 6
- rac-1-O-oleyl-2-O-palmitoylglyceryl-3-phosphoryl captopril-p-methoxybenzyl ester,
rac-1-O-oleyl-2-O-palmitoylglyceryl-3-phosphoryl captopril-2,4,6-trimethylbenzyl ester,
rac-1-O-oleyl-2-O-palmitoylglyceryl-3-phosphoryl captopril phthalimido methyl ester,
rac-1-O-oleyl-2-O-acetylglyceryl-3-phosphoryl captopril-p-nitrobenzyl ester,
- 5 rac-1-O-oleyl-2-O-acetylglyceryl-3-phosphoryl captopril ethyl ester,
 rac-1-O-oleyl-2-O-acetylglyceryl-3-phosphoryl captopril methyl ester,
 rac-1-O-oleyl-2-O-acetylglyceryl-3-phosphoryl captopril benzylester,
 rac-1-O-oleyl-2-O-acetylglyceryl-3-phosphoryl captopril benzoyl ester,
 rac-1-O-oleyl-2-O-acetylglyceryl-3-phosphoryl captopril isopropyl ester,
- 10 rac-1-O-oleyl-2-O-acetylglyceryl-3-phosphoryl captopril-n-butyl ester,
 rac-1-O-oleyl-2-O-acetylglyceryl-3-phosphoryl captopril-t-butyl ester,
 rac-1-O-oleyl-2-O-acetylglyceryl-3-phosphoryl captopril cyclohexyl ester,
 rac-1-O-oleyl-2-O-acetylglyceryl-3-phosphoryl captopril pentyl ester,
 rac-1-O-oleyl-2-O-acetylglyceryl-3-phosphoryl captopril-p-toluenesulfonyl ester,
- 15 rac-1-O-oleyl-2-O-acetylglyceryl-3-phosphoryl captopril-p-methoxybenzyl ester,
 rac-1-O-oleyl-2-O-acetylglyceryl-3-phosphoryl captopril-2,4,6-trimethylbenzyl ester,
 rac-1-O-oleyl-2-O-acetylglyceryl-3-phosphoryl captopril phthalimido methyl ester,
 rac-1-O-octadecyl-2-O-palmitoylglyceryl-3-phosphoryl captopril-p-nitrobenzyl ester,
 rac-1-O-octadecyl-2-O-palmitoylglyceryl-3-phosphoryl captopril ethyl ester,
- 20 rac-1-O-octadecyl-2-O-palmitoylglyceryl-3-phosphoryl captopril methyl ester,
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 rac-1-O-octadecyl-2-O-palmitoylglyceryl-3-phosphoryl captopril-n-butyl ester,
- 25 rac-1-O-octadecyl-2-O-palmitoylglyceryl-3-phosphoryl captopril-t-butyl ester,
 rac-1-O-octadecyl-2-O-palmitoylglyceryl-3-phosphoryl captopril cyclohexyl ester,
 rac-1-O-octadecyl-2-O-palmitoylglyceryl-3-phosphoryl captopril pentyl ester,
 rac-1-O-octadecyl-2-O-palmitoylglyceryl-3-phosphoryl captopril-p-toluenesulfonyl ester,
 rac-1-O-octadecyl-2-O-palmitoylglyceryl-3-phosphoryl captopril-p-methoxybenzyl ester,

rac-1-O-octadecyl-2-O-palmitoylglyceryl-3-phosphoryl captopril-2,4,6-trimethylbenzyl ester.

rac-1-O-octadecyl-2-O-palmitoylglyceryl-3-phosphoryl captopril phthalimido methyl ester.

5 rac-1-O-octadecyl-2-O-acetylglyceryl-3-phosphoryl captopril-p-nitrobenzyl ester,

rac-1-O-octadecyl-2-O-acetylglyceryl-3-phosphoryl captopril ethyl ester,

rac-1-O-octadecyl-2-O-acetylglyceryl-3-phosphoryl captopril methyl ester,

rac-1-O-octadecyl-2-O-acetylglyceryl-3-phosphoryl captopril benzyl ester,

rac-1-O-octadecyl-2-O-acetylglyceryl-3-phosphoryl captopril benzoyl ester.

10 rac-1-O-octadecyl-2-O-acetylglyceryl-3-phosphoryl captopril isopropyl ester,

rac-1-O-octadecyl-2-O-acetylglyceryl-3-phosphoryl captopril-n-butyl ester,

rac-1-O-octadecyl-2-O-acetylglyceryl-3-phosphoryl captopril-t-butyl ester,

rac-1-O-octadecyl-2-O-acetylglyceryl-3-phosphoryl captopril cyclohexyl ester,

rac-1-O-octadecyl-2-O-acetylglyceryl-3-phosphoryl captopril pentyl ester,

15 rac-1-O-octadecyl-2-O-acetylglyceryl-3-phosphoryl captopril-p-toluenesulfonyl ester,

rac-1-O-octadecyl-2-O-acetylglyceryl-3-phosphoryl captopril-p-methoxybenzylester,

rac-1-O-octadecyl-2-O-acetylglyceryl-3-phosphoryl captopril-2,4,6-trimethylbenzyl ester,

rac-1-O-octadecyl-2-O-acetylglyceryl-3-phosphoryl captopril phthalimido methyl ester,

20 rac-1-S-cetyl-2-O-acetylthioglyceryl-3-phosphoryl captopril-p-nitrobenzyl ester,

rac-1-S-cetyl-2-O-acetylthioglyceryl-3-phosphoryl captopril ethyl ester,

rac-1-S-cetyl-2-O-acetylthioglyceryl-3-phosphoryl captopril methyl ester,

rac-1-S-cetyl-2-O-acetylthioglyceryl-3-phosphoryl captopril benzyl ester,

rac-1-S-cetyl-2-O-acetylthioglyceryl-3-phosphoryl captopril benzoyl ester,

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rac-1-S-cetyl-2-O-acetylthioglyceryl-3-phosphoryl captopril pentyl ester,

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rac-1-S-cetyl-2-O-acetylthioglyceryl-3-phosphoryl captopril-2,4,6-trimethylbenzyl
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- 5 rac-1-S-cetyl-2-O-acetylthioglyceryl-3-phosphoryl captopril-phthalimido methyl ester,
rac-1-S-oleyl-2-O-palmitoylthioglyceryl-3-phosphoryl captopril-p-nitrobenzyl ester,
rac-1-S-oleyl-2-O-palmitoylthioglyceryl-3-phosphoryl captopril ethyl ester,
rac-1-S-oleyl-2-O-palmitoylthioglyceryl-3-phosphoryl captopril methyl ester,
rac-1-S-oleyl-2-O-palmitoylthioglyceryl-3-phosphoryl captopril benzyl ester,
10 rac-1-S-oleyl-2-O-palmitoylthioglyceryl-3-phosphoryl captopril benzoyl ester,
rac-1-S-oleyl-2-O-palmitoylthioglyceryl-3-phosphoryl captopril isopropyl ester,
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rac-1-S-oleyl-2-O-acetylthioglyceryl-3-phosphoryl captopril ethyl ester,
25 rac-1-S-oleyl-2-O-acetylthioglyceryl-3-phosphoryl captopril methyl ester,
rac-1-S-oleyl-2-O-acetylthioglyceryl-3-phosphoryl captopril benzyl ester,
rac-1-S-oleyl-2-O-acetylthioglyceryl-3-phosphoryl captopril benzoyl ester,
rac-1-S-oleyl-2-O-acetylthioglyceryl-3-phosphoryl captopril isopropyl ester,
rac-1-S-oleyl-2-O-acetylthioglyceryl-3-phosphoryl captopril-n-butyl ester,

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rac-1-S-octadecyl-2-O-palmitoylthioglyceryl-3-phosphoryl captopril methyl ester,
rac-1-S-octadecyl-2-O-palmitoylthioglyceryl-3-phosphoryl captopril benzyl ester,
rac-1-S-octadecyl-2-O-palmitoylthioglyceryl-3-phosphoryl captopril benzoyl ester,
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rac-1-S-octadecyl-2-O-palmitoylthioglyceryl-3-phosphoryl captopril-n-butyl ester,
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25 benzyl ester,
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- rac-1-S-octadecyl-2-O-acetylthioglyceryl-3-phosphoryl captopril methyl ester,
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10 ester.
rac-1-S-octadecyl-2-O-acetylthioglyceryl-3-phosphoryl captopril-p-methoxybenzyl
ester,
rac-1-S-octadecyl-2-O-acetylthioglyceryl-3-phosphoryl captopril-2,4,6-trimethylbenzyl
ester,
15 rac-1-S-octadecyl-2-O-acetylthioglyceryl-3-phosphoryl captopril phthalimido methyl
ester, or their pharmacologically acceptable salts.

In this invention, the most important point for development of transdermal therapeutic agent is to increase the absorption through transdermal route. Because the skin cell membrane of the human body consists of phospholipid layer, the lipophilic compounds have greater propensity to be absorbed from skin to the body.

These conjugates represented in this invention can easily penetrate through skin cell consisting of double layer of phospholipid, because these compounds are phospholipid conjugates with lipophilic physicochemical properties. It is also possible to maintain steady, ideal plasma concentrate of these drugs, because of the inherent mechanism of transdermal controlled delivery of a drug.

The absorbed material through the skin is hydrolyzed to ACE inhibitor and phospholipid part by lysophospholipase in the body. The phospholipid part is converted to the platelet activating factor via a biosynthesis route and then it express blood pressure regulatory action and the ACE inhibitor part of the molecule exhibits its blood pressure

11

lowering activity by inhibiting the conversion of angiotensin I to angiotensin II.

Therefore, because each component of hydrolyzed phospholipid and ACE inhibitor conjugate has blood pressure controlling function, new compounds having two parts are expected to possess favorable pharmacological activity and also have superior blood pressure lowering activity.

The following examples are detailed illustrative of this invention.

EXAMPLE 1

Rac-1-O-octadecyl-2-O-palmitoyl-glyceryl-3-phosphoryl captopril-p-nitrobenzyl ester

10 Dissolve 4.55 g (0.01 mol) of 3-S-thiophosphoryl-2-D-methylpropanoyl-L-proline-p-nitrobenzyl ester and 7 g (0.012 mol) of rac-1-O-octadecyl-2-O-palmitoylglycerol in 350 ml of anhydrous pyridine and concentrate to 2/3 of volume in vacuo. 6.8 g (0.033 mol) of dicyclohexylcarbodiimide is added, the mixture is heated at 75 ~ 80°C for 4 days, then concentrate reaction mixture in vacuo.

15 To the residue 600ml of ethyl ether and 350ml of distilled water are added. Then the solution is adjusted the pH to 0 ~ 1 with 10ml of 10% hydrochloric acid and stirred overnight. Filter, then the organic phase is dried and concentrated in vacuo. Chromatography with chloroform- methanol(9 : 1) mixture affords 3.61g of the desired product.

20 m.p. : 44 ~ 45 °C

TLC R_f 0.45 (chloroform : methanol = 5 : 1)

NMR (CDCl₃) δ 0.87(6, t, 2CH₃), 1.10-1.57(61, m, 29CH₂, CH₃), 2.03(2, t, CH₂CO), 2.30(2, t, CH₂CO), 3.05-3.25(4, t, OCH₂, proline NCH₂), 3.45(2, t, OCH₂), 3.62-3.75(4, m, CH₂O, SCH₂), 3.85-4.20(2, d, CH₂OP), 4.70(1, t, proline CH), 5.16-5.26(3, m, CCHC, benzyl CH₂), 7.52(2, d, C₆H₄), 8.20(2, d, C₆H₄)

IR : (KBr) 2918, 2850, 1739, 1641, 1525, 1346, 1168, 1078 cm⁻¹

WO 93/11136

12

EXAMPLE 2

Rac-1-O-octadecyl-2-O-palmitoyl-glyceryl-3-phosphoryl captopril

Dissolve 0.5 g (0.5 mmol) of rac-1-O-octadecyl-2-O-palmitoyl-3-phosphorylcaptopril-p-nitrobenzyl ester in 30mL of methylenechloride and add 180mL of 5 1N sulfuric acid solution, 20mL of methanol, and 2.2 g of zinc powder. After stirring overnight, wash the reaction mixture with 80mL of distilled water. Dry on anhydrous sodium sulfate, filter through celite, concentrate in vacuo. After purification by preparative thin layer chromatography with chloroform-methanol (5 : 1). 0.28g(yield 64.94%) of white powder is obtained as the desired product.

10 m.p. : 66~68 °C

TLC R_f 0.45 (chloroform : methanol = 3 : 1)

NMR (CDCl₃) δ 15 0.87(6, t, 2CH₃), 1.11-1.65(61, m, 29CH₂, CH₃),
1.85-2.17(2, t, CH₂CO), 2.35(2, t, CH₂CO),
2.95-3.75(12, m, CH₂CH₂, proline NCH₂, OCH₂, CH₂O, SCH₂),
3.45(2, t, OCH₂), 3.62-3.75(4, m, CH₂O, SCH₂),
3.85-4.02(2, d, CH₂OP), 4.18(1, t, proline CH), 5.19(1, m, CCHC)

IR : (KBr) 3379, 2918, 2850, 1737, 1610, 1170, 1078 cm⁻¹EXAMPLE 3

20 Rac-1-O-octadecyl-2-O-acetyl-glyceryl-3-phosphoryl captopril-p-nitrobenzyl ester

Dissolve 8.52 g (19.71 mmol) of 3-S-thiophosphoryl-2-D-methylpropanoyl-L-proline-p-nitrobenzyl ester and 7.9 g (20.43 mmol) of rac-1-O-octadecyl-2-O-acetylglycerol in 400mL of anhydrous pyridine and concentrate to 2/3 of volume in vacuo.

After adding 12 g (63.38 mmol) of dicyclohexylcarbodiimide, the reaction mixture is heated at 70~80 °C for 4 days and concentrate in vacuo.

To the residue 600mL of ethyl ether and 350mL of distilled water are added. Then mixture is adjusted the pH to 0~1 with 30mL of 10% hydrochloric acid and stirred overnight. Filter, then the organic phase is dried and concentrated in vacuo. Chromatography with chloroform-methanol(9 : 1) affords 3.18g of yellow amorphous

13

powder as the desired product.

m.p. : 37 ~ 38°C

TLC R_f 0.35 (chloroform : methanol = 5 : 1)

NMR (CDCl₃) δ 0.87(6, t, 2CH₃), 1.12-1.57(35, m, 16CH₂, CH₃),

5 1.73-2.40(7, m, CH₂CH₂, CH₃CO),

2.61-3.15(4, m, OCH₂, proline NCH₂),

3.49-4.18(2, m, OCH₂, CH₂O, SCH₂, CH₂OP),

4.61(1, t, proline CH), 5.16-5.38(3, m, CCHC, benzyl CH₂),

7.52(2, d, C₆H₄), 8.20(2, d, C₆H₄)

10 IR : (KBr) 2922, 2852, 1739, 1639, 1525, 1346, 1240, 1166, 1076 cm⁻¹

EXAMPLE 4

Rac-1-O-octadecyl-2-O-acetyl-glyceryl-3-phosphoryl captopril

Dissolve 0.43 g (0.53 mmol) of rac-1-O-octadecyl-2-O-acetyl glyceryl-3-phosphoryl captopril-p-nitrobenzyl ester in 30ml of methylenechloride and add 180ml of 1N sulfuric acid solution, 20ml of methanol, and 3.2 g of zinc powder.

15 After stirring overnight, wash reaction mixture with 80ml of distilled water. Dry on anhydrous sodium sulfate, filter through celite, concentrate in vacuo. After purification by preparative thin layer chromatography with chloroform-methanol (5 : 1), 0.26g(yield 72.63%) of white powder is obtained as the desired product.

20 m.p. : 58 ~ 60 °C

TLC R_f 0.10 (chloroform : methanol = 3 : 1)

NMR (CDCl₃) δ 0.87(3, t, CH₃), 1.11-1.65(35, m, 16CH₂, CH₃),

25 1.85-2.30(7, m, CH₂CH₂, CH₃CO),

2.95-3.75(8, m, OCH₂, proline NCH₂, CH₂O, SCH₂),

3.85-4.15(2, d, CH₂OP), 4.28(1, t, proline CH), 5.19(1, m, CCHC)

IR : (KBr) 3373, 2918, 2850, 1737, 1606, 1240, 1078 cm⁻¹

EXAMPLE 5

14

Rac-1-S-octadecyl-2-O-palmitoyl-thioglyceryl-3-phosphoryl captopril-p-nitrobenzyl ester

Dissolve 0.32 g (10 mmol) of 3-S-thiophosphoryl-2-D-methylpropanoyl-L-proline-p-nitrobenzyl ester and 5.97 g (10 mmol) of rac-1-S-octadecyl-2-O-palmitoyl-1-thioglycerol in 350ml of anhydrous pyridine and concentrate to 2/3 of volume in vacuo.

- 5 After adding 6.8 g (33 mmol) of dicyclohexylcarbodiimide, reaction mixture is heated at 70°C to 80°C for 4 days and concentrate in vacuo.

To the residue in 500ml of ethyl ether and 300ml of distilled water are added.

Then mixture is adjusted the pH to 0 ~ 1 with 20ml of 10% hydrochloric acid and stirred overnight. Filter, then the organic phase is dried and concentrate in vacuo.

- 10 Chromatography with chloroform-methanol(9 : 1) affords 1.6 g(yield 15.79%) of pale yellow powder as the desired product

m.p. : 46 ~ 47 °C

TLC R_f 0.52 (chloroform : methanol = 5 : 1)

NMR (CDCl₃) δ 0.89(6, t, 2CH₃), 1.10-1.65(61, m, 29CH₂, CH₃),
15 2.03(7, m, CH₂CH₂, CH₃CO), 2.23-2.89(6, m, CH₂CO, CH₂SCH₂),

3.04(2, m, proline NCH₂),

3.65-3.80(2, m, SCH₂), 4.40(2, d, CH₂OPCH₂OP),

4.68(1, t, proline CH), 5.11-5.35(3, m, CCHC, benzyl CH₂),

7.52(2, d, C₆H₄), 8.20(2, d, C₆H₄)

- 20 IR : (KBr) 2918, 2850, 1737, 1641, 1525, 1348, 1170, 1078 cm⁻¹

EXAMPLE 6

Rac-1-S-octadecyl-2-O-palmitoyl-thioglyceryl-3-phosphoryl captopril

- Dissolve 0.5 g (0.49 mmol) of rac-1-S-octadecyl-thioglyceryl-3-phosphorylcaptopril-p-nitrobenzyl ester in 30ml of methylenechloride and add 180ml of 25 1N sulfuric acid solution, 20ml of methanol, and 2.2 g of zinc powder. After stirring overnight, wash the reaction mixture with 80ml of distilled water, dry on anhydrous sodium sulfate, filter through celite, concentrate in vacuo. After purification by preparative thin layer chromatography with chloroform-methanol (5 : 1), 0.12 g(yield

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27.88%) of white powder is obtained as the desired product.

m.p. : 68 ~ 70°C

TLC R_f 0.47 (chloroform : methanol = 3 : 1)

NMR (CDCl₃) δ 0.88(6, t, 2CH₃), 1.12-1.65(61, m, 29CH₂, CH₃),

5 1.85-2.27(4, m, CH₂CH₂), 2.35(2, t, CH₂CO),

2.45-2.90(5, m, CH₂S'CH₂, CCHCO), 3.04(2, m, proline NCH₂),

3.65(2, m, SCH₂), 4.05(2, d, CH₂OP), 4.31(1, t, proline CH),

5.19(1, m, CCHC)

IR : (KBr) 3373, 2918, 2850, 1737, 1604, 1076 cm⁻¹

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EXAMPLE 7

Rac-1-S-octadecyl-2-O-acetyl-thioglyceryl-3-phosphoryl captopril-p-nitrobenzyl ester

Dissolve 5.6 g (12.95 mmol) of 3-S-thiophosphoryl-2-D-methylpropanoyl-L-proline-p-nitrobenzyl ester and 5.33 g (13.23 mmol) of rac-1-S-octadecyl-2-O-acetylthioglycerol in 300mL of anhydrous pyridine and concentrate to 2/3 of volume in vacuo. After adding 7.8 g (37.80 mmol) of dicyclohexylcarbodiimide, the reaction mixture is heated at 70 ~ 80°C for 4 days and concentrate in vacuo.

To the residue in 600mL of ethyl ether and 350mL of distilled water are added.

Then the mixture is adjusted the pH to 0 ~ 1 with 30mL of 10% hydrochloric acid and 20 stirred overnight. Filter, then the organic phase is dried and concentrate in vacuo. Chromatography with chloroform-methanol(9 : 1) affords 1.2 g(yield 11.34%) of yellow amorphous powder as the desired product.

m.p. : 35 ~ 36°C

TLC R_f 0.38 (chloroform : methanol = 5 : 1)

25 NMR (CDCl₃) δ 0.87(3, t, CH₃), 1.10-1.63(35, m, 16CH₂, CH₃),

1.92-2.40(7, m, CH₂CH₂, CH₃CO), 2.52(4, t, CH₂SCH₂),

2.61-3.15(2, m, proline NCH₂), 3.65-3.80(2, m, SCH₂),

4.00(2, d, CH₂OP), 4.68(1, t, proline CH),

5.11-5.35(3, m, CCHC, benzyl CH₂), 7.52(2, d, C₆H₄).

16

8.20(2, d, C₆H₄)IR : (KBr) 2922, 2852, 1739, 1641, 1523, 1346, 1167, 1074 cm⁻¹EXAMPLE 8

5 Rac-1-S-octadecyl-2-O-acetyl-thioglyceryl-3-phosphorylcaptopril

Dissolve 0.3 g (0.36 mmol) of rac-1-S-octadecyl-2-O-acetyl-thioglyceryl-3-phosphorylcaptopril-p-nitrobenzyl ester in 30mL of methylenechloride and add 180mL of 1N sulfuric acid solution, 20mL of methanol, and 2.2 g of zinc powder. After stirring overnight, wash the reaction mixture with 80 mL of distilled water. Dry on anhydrous sodium sulfate, filter through celite, concentrate in vacuo. After purification by preparative thin layer chromatography with chloroform-methanol (5 : 1), 0.11 g(yield 43.96%) of white powder is obtained as the desired product.

10 m.p. : 61 - 63 °C

15 TLC R_f 0.12 (chloroform : methanol = 3 : 1)

15 NMR (CDCl₃) δ 0.88(3, t, CH₃), 1.13-1.65(35, m, 16CH₂, CH₃),
1.81-2.35(7, m, CH₂CH₂, CH₃CO), 2.52(4, m, CH₂SCH₂),
2.70-3.10(2, m, proline NCH₂), 3.65-3.80(2, m, SCH₂),
4.00(2, d, CH₂OP), 4.32(1, t, proline CH), 5.12(1, m, CCHC)

IR : (KBr) 3373, 2918, 2850, 1739, 1610, 1078 cm⁻¹

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EXPERIMENTAL EXAMPLE

The inhibitory activity of angiotensin converting enzyme for the compounds of this invention prepared by above examples was determined as follows ;

The inhibitory activity was determined by using a modification of the method of

25 Cushman, et al. [Biochemical Pharmacology, 20, 1637(1971)] Rabbit lung acetone powder was extracted with 10 volumes of 50 mM sodium borate buffer solution(pH 8.3) by homogenization at 4°C and centrifuged for 40 minutes at 40,000 × g.

The supernatant which contained angiotensin converting enzyme was used for ACE assay. Hippuryl-L-histidyl-L-leucine(HHL) was used as a substrate of enzymatic

17

reaction and the reaction was determined in 13 x 100 mm of test tube.

The assay mixture (total volume, 0.25 ml) consisted of 50 mM sodium borate buffer (pH 8.3), 300 mM sodium chloride, and 5 mM HHL(pH 8.3), and they were reacted by addition of 0 ~ 10 mU of rabbit lung acetone powder extract for 30 minutes at 5 37°C.

The volume of enzyme extract was 0.15 ml or below and the reaction solution was preincubated at 37°C for 30 minutes without the substrate and after adding HHL, reacted for 30 minutes, the reaction was terminated by addition of 0.25 ml of 1N-HCl aqueous sloution

10 In the case of blank assay, hydrochloric acid was added before adding the enzyme extract. Hippuric acid was extracted with 1.5 ml of ethyl acetate which was separated by centrifuging at 3,000 rpm for 10 minutes. 1.0 ml of ethyl acetate layer was transferred into the test tube and evaporated at 90°C for 1 hour on temp-block.

15 Hippuric acid was dissolved in 1.0 ml of 50 mM sodium borate buffer (pH 8.3) and qualified from its absorbance at 228 nm. The final concentration of inhibitor was adjusted to 2×10^4 , 2×10^5 μ M with sodium borate buffer solution(pH 8.3) and reaction solution without the substrate was preincubated for 30 minutes and after adding the substrate, it was reacted at 37°C for 30 minutes and terminated with 1N-HCl.

20 The synthesized inhibitors with non-water soluble property were dissolved by ultrasonic treatment. Angiotensin converting enzyme inhibitory activity is compared with captopril.

[TEST RESULTS]

25 The test results obtained for the compound of example 1, 2, 3, 4, 5, 6, 7 and 8 are shown in table below :

	Example No. of Compound	Concentration(μM)	
		2 × 10 ⁻⁴	2 × 10 ⁻⁵
5	Compound 1	77%	39%
	Compound 2	97%	80%
	Compound 3	85%	60%
	Compound 4	98%	98%
	Compound 5	31%	4%
	Compound 6	92%	70%
	Compound 7	78%	43%
	Compound 8	90%	80%
10	Captopril	94%	91%
	Compound 1 : rac-1-O-octadecyl-2-O-palmitoyl-glyceryl-3-phosphorylcaptopril-p-nitrobenzyl ester		
	Compound 2 : rac-1-O-octadecyl-2-O-palmitoyl-glyceryl-3-phosphoryl captopril		
	Compound 3 : rac-1-O-octadecyl-2-O-acetyl-glyceryl-3-phosphoryl captopril-p-nitrobenzyl ester		
	Compound 4 : rac-1-O-octadecyl-2-O-acetyl-glyceryl-3-phosphoryl captopril		
	Compound 5 : rac-1-S-octadecyl-2-O-palmitoyl-thioglyceryl-3-phosphoryl captopril-p-nitrobenzyl ester		
	Compound 6 : rac-1-S-octadecyl-2-O-palmitoyl-thioglyceryl-3-phosphoryl captopril		
	Compound 7 : rac-1-S-octadecyl-2-O-acetyl-thioglyceryl-3-phosphoryl captopril-p-nitrobenzyl ester		
	Compound 8 : rac-1-S-octadecyl-2-O-acetyl-thioglyceryl-3-phosphoryl captopril.		

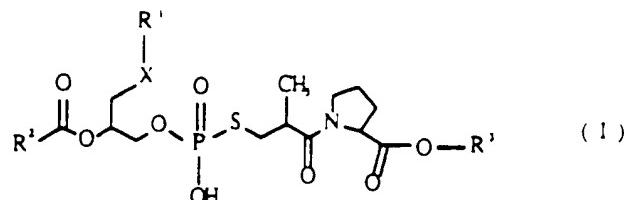
- 15
- Compound 1 : rac-1-O-octadecyl-2-O-palmitoyl-glyceryl-3-phosphorylcaptopril-p-nitrobenzyl ester
- Compound 2 : rac-1-O-octadecyl-2-O-palmitoyl-glyceryl-3-phosphoryl captopril
- Compound 3 : rac-1-O-octadecyl-2-O-acetyl-glyceryl-3-phosphoryl captopril-p-nitrobenzyl ester
- 20 Compound 4 : rac-1-O-octadecyl-2-O-acetyl-glyceryl-3-phosphoryl captopril
- Compound 5 : rac-1-S-octadecyl-2-O-palmitoyl-thioglyceryl-3-phosphoryl captopril-p-nitrobenzyl ester
- Compound 6 : rac-1-S-octadecyl-2-O-palmitoyl-thioglyceryl-3-phosphoryl captopril
- 25 Compound 7 : rac-1-S-octadecyl-2-O-acetyl-thioglyceryl-3-phosphoryl captopril-p-nitrobenzyl ester
- Compound 8 : rac-1-S-octadecyl-2-O-acetyl-thioglyceryl-3-phosphoryl captopril.

From the results above expressed it can be concluded that the new compounds mentioned in this invention possess antihypertensive activity at least equivalent to that of 30 captopril and these compounds have lipophilic activity which permits their transdermal delivery resulting in superior antihypertensive effect.

WHAT IS CLAIMED IS :

1. New pyrrolidine derivatives and salts represented by formula (I) as below

5



wherein,

R^1 is saturated or unsaturated alkyl of 2 to 20 carbon atoms, or aryl group;

R^2 is saturated or unsaturated alkyl of 1 to 17 carbon atoms, or aryl group;

10 R^3 is hydrogen atom, saturated or unsaturated alkyl of 1 to 20

carbon atoms, or aryl group or its derivatives; and

X is oxygen or sulfur atom.

2. The pyrrolidine derivatives according to claim 1, wherein R^1 is octadecyl, oleyl,

15 cetyl, methyl, ethyl, dodecyloxy, methylphenyl or sulfonyloctyl group.

3. The pyrrolidine derivatives according to claim 1, wherein R^2 is methyl, ethyl,

propyl, butyl, heptadecyl, pentadecyl, oleyl or cetyl.

20 4. The pyrrolidine derivatives according to claim 1, wherein R^3 is hydrogen, methyl,

ethyl, propyl, isopropyl, butyl, pentyl, cyclohexyl, benzoyl, benzyl, p-nitrobenzyl,

toluenesulfonyl, p-methoxybenzyl, 2,4,6-trimethylbenzyl or phthalimidomethyl

group.

25 5. The pyrrolidine derivatives according to claim 1, wherein the compound of

formula (I) is rac-1-O-octadecyl-2-O-palmitoylglyceryl-3-phosphoryl captopril-

p-nitrobenzyl ester.

- 5

6. The pyrrolidine derivatives according to claim 1, wherein the compound of formula (I) is rac-1-S-octadecyl-2-O-palmitoylthioglyceryl-3-phosphoryl captoril-p-nitrobenzyl ester.

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7. The pyrrolidine derivatives according to claim 1, wherein the compound of formula (I) is rac-1-O-octadecyl-2-O-palmitoylglyceryl-3-phosphoryl captoril.

15

8. The pyrrolidine derivatives according to claim 1, wherein the compound of formula (I) is rac-1-S-octadecyl-2-O-palmitoylthioglyceryl-3-phosphoryl captoril.

20

9. The pyrrolidine derivatives according to claim 1, wherein the compound of formula (I) is rac-1-O-octadecyl-2-O-acetylthioglyceryl-3-phosphoryl captoril-p-nitrobenzyl ester.

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10. The pyrrolidine derivatives according to claim 1, wherein the compound of formula (I) is rac-1-S-octadecyl-2-O-acetylthioglyceryl-3-phosphoryl captoril-p-nitrobenzyl ester.

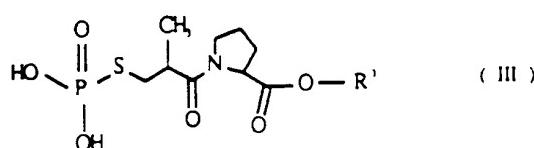
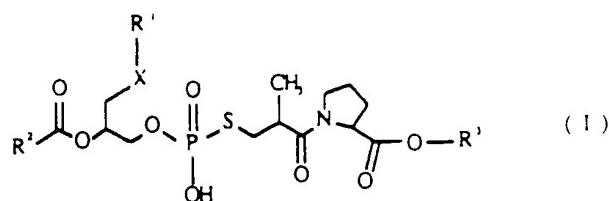
11. The pyrrolidine derivatives according to claim 1, wherein the compound of formula (I) is rac-1-O-octadecyl-2-O-acetylthioglyceryl-3-phosphoryl captoril.

25

12. The pyrrolidine derivatives according to claim 1, wherein the compound of formula (I) is rac-1-S-octadecyl-2-O-acetylthioglyceryl-3-phosphoryl captoril.

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13. A method for preparing new pyrrolidine derivatives or their salts of formula (I) by condensation of compound of formula (II) with compound of formula (III) in anhydrous basic solvent using condensing agent

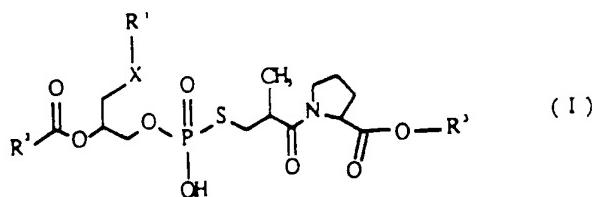


wherein,

5 R^1, R^2, R^3 and X each are as defined in claim 1.

14. The method according to claim 13, wherein pyridine, triethylamine or ethylamine is used as anhydrous base.
 15. The method according to claim 13, wherein dicyclohexylcarbodiimide, 2,4,6-triisopropylbenzenesulfonylchloride, 1-(2,4,6-triisopropylbenzenesulfonyl)imidazole, 1-(2,4,6-triisopropylbenzenesulfonyl)-3-nitro-1,2,4-triazole or 2-ethoxy-1-(2H)-quinoline carboxylic acid ester is used as condensing agent.
 16. The method according to claim 13, wherein said condensation is carried out at 40-~100°C.
 17. A pharmaceutical composition useful in the treatment of hypertension containing pyrrolidine derivatives and their salts of formula(I) as below

WO 93/11136

22

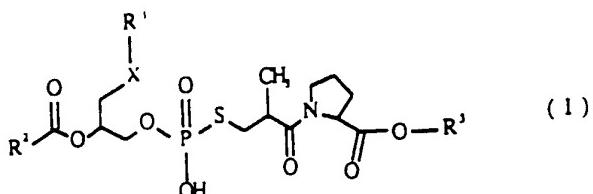
wherein,

 R^1, R^2, R^3 and X each are as defined in claim 1.

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18. A formulation for transdermal administration containing pyrrolidine derivatives or their salts of formula (I) as a pharmacologically active component for antihypertension

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wherein,

 R^1, R^2, R^3 and X each are as defined in claim 1.

15

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 92/00066

A. CLASSIFICATION OF SUBJECT MATTER

IPC⁵ : C 07 F 9/165; A 61 K 31/675
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁵ : C 07 F 9/09, 9/10, 9/16, 9/165; A 61 K 31/66, 31/675

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS/DARC, WPIL(QUESTEL)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP, A2, 0 312 041 (URIACH & CIA) 19 April 1989 (19.04.89), see claims 1,15,16; examples 47-51.	1,17
A	US, A, 4 595 681 (SNYDER et al.) 17 June 1986 (17.06.86), see claim 1.	1,17
A	Biochemical and Biophysical Research Communications, vol. 85, no. 2, issued 1978, November 29, New York & London, M. MacCoss et al. "The Synthesis, Characterization, and Preliminary Biological Evaluation of 1-β-D-Arabinofuranosylcytosine-5'-Diphosphate-L-1,2-Dipalmitin", pages 714-723; see summary.	1,17
A	Journal of Medicinal Chemistry, vol. 25, no. 11, issued 1982, November, Am.Chem.Soc., E.K. Ryu et al. "Phospholipid-Nucleoside Conjugates. Syntheses and Preliminary Biological Evaluation of 1-β-D-Arabinofuranosylcytosine 5'-Monophosphate-L-1,2-Dipalmitin and Selected 1'-β-D-Arabinofuranosylcytosine 5'-Diphosphate-L-1,2-Diacylglycerols" pages 1322-1329; see summary.	1,17

Further documents are listed in the continuation of Box C.

See patent family annex.

- * Special categories of cited documents:
 - "A" document defining the general state of the art which is not considered to be of particular relevance
 - "E" earlier document but published on or after the international filing date
 - "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reasons (as specified)
 - "O" document referring to an oral disclosure, use, exhibition or other means
 - "P" document published prior to the international filing date but later than the priority date claimed
- T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search 19 January 1993 (19.01.93)	Date of mailing of the international search report 21 January 1993 (21.01.93)
Name and mailing address of the ISA/AT AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 Vienna Facsimile No. 0222/53424/535	Authorized officer MARCHART e.h. Telephone No. 0222/53424/137

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/KR 92/00066

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
EP A2 312041		ES UA 1003711 ES YA 1003711	01-08-88 01-03-89
US A 4595681	17-06-86	keine - none - rien	